MEMORANDUM June 14, 2001

SUBJECT: **para-Chloroaniline Hydrochloride (Diflubenzuron, Dimilin)** Quantitative Risk Assessment (Q_1^*) Based On $B6C3F_1$ Mouse Gavage Study With mg/kg Body Weight$^{3/4}$/Day Interspecies Scaling Factor

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Conclusion

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, for para-Chloroaniline Hydrochloride based upon male mouse liver adenoma and/or carcinoma combined tumor rates is 1.12×10^{-1} in human equivalents. The dose levels used from the 104-week gavage study were 0, 3, 10, and 30 mg/kg/day of para-Chloroaniline Hydrochloride. The corresponding tumor rates were 11/50, 21/49, 20/50, and 21/50, respectively.

Background

On March 16, 1995, the HED RfD/Peer Review Committee evaluated the toxicology and carcinogenicity data of Diflubenzuron. At that meeting the Committee also evaluated the carcinogenicity of para-Chloroaniline Hydrochloride, a known metabolite of Diflubenzuron. The Committee classified para-Chloroaniline Hydrochloride as a Group B2 Carcinogen - probable human carcinogen, based on the evidence of carcinogenicity in rats and mice (NTP Studies). The Committee further concluded that it was not necessary to convene the Carcinogenicity Peer Review Committee to confirm this classification. (Memorandum: RfD/Peer Review Report of Diflubenzuron [1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl) urea], G.Ghali, HED to D. Edwards, RD and E. Saito, SRRD, dated April 27, 1995). The Committee, however, did not recommend the methodology for quantification of human risk

In 1994, a unit risk, Q_1^*, of 6.38×10^{-2}, based on the sarcomas of the spleen in male rats using the mg/kg body weight$^{3/4}$/day interspecies scaling factor was calculated for para-Chloroaniline Hydrochloride (Memoradum: P-Chloroaniline (Dimilin Metabolite) - Quantitative Risk, Q_1^*, (Updated) from NTP Rat Oncogenicity Study, B. Fisher to H. Spencer, dated November 28, 1994).

On February 7 and May 8, 2001, the Metabolism Assessment Review Committee (MARC) evaluated the residues of concern for Diflubenzuron dietary cancer risk assessment. At these meetings, the MARC determined that the dietary cancer risk assessment for para-Chloroaniline Hydrochloride, a Diflubenzuron metabolite, should be assessed, the assessment should be based on the Q_1^* calculated for both the sarcomas of the spleen in rats and the liver tumors in mice, and that the most potent Q_1^* will used for the purpose of lifetime cancer risk assessment by the Agency (Memorandum: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Meetings of 2/20/01 & 5/8/01. **Diflubenzuron.** Residues of Concern for Cancer Risk Assessment. Chemical 108201. Barcode D272976. Case 239100. Submission S590172. G. Kramer to Y. Donovan, Executive Secretary, MARC, dated May 31, 2001). Consequently, a Q_1^* of 1.12×10^{-1} based on male mouse liver adenoma and/or carcinoma combined tumor rates was the most potent of those calculated.

All unit risks have been converted from animals to humans by use of the $^3/_4$ interspecies scaling factor (Tox_Risk program, Version 3.5, K. Crump, 1994)[1]. For the conversion to human equivalents, weights of 0.03 kg for the mouse, 70 kg for humans, and the use of 104 weeks for the mouse life-span were used.

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, the true value of the risk is unknown, and may be as low as zero.

Dose-Response Analysis

Male mice showed no statistically significant incremental changes in mortality with increasing doses of para-Chloroaniline Hydrochloride. The unit risk, Q_1^*, was obtained by the application of the Multistage model (Tox_Risk program, Version 3.5, K. Crump, 1994).

Male mice had statistically significant differences in the pair-wise comparisons of all dosed groups with the controls for liver adenomas and/or carcinomas combined, all at $p < 0.05$, however, there was not a significant trend.